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Dr. William Eaton Oral History 2020

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Interview with Dr. William Eaton

Conducted on January 6, 2020 by Kenneth Dur**r**

Kenneth Durr:

This is an interview with Dr. William Eaton. Today is January 6th, 2020, and I'm Kenneth Durr. Dr. Eaton, thanks for taking time to talk today.

William Eaton:

My pleasure.

Kenneth Durr:

I want to start with some background, and I want to dig into yours just a little bit. You're from Philadelphia, right?

William Eaton:

Yes.

Kenneth Durr:

Tell me a little about your family, your upbringing, and what got you toward science.

William Eaton:

I came from what I call a financially poor, but intellectually rich family. My mother could have been the first woman to ever get an advanced degree in the classics from the University of Pennsylvania. She got a master's degree in Latin in 1927. She motivated all five of us children - I had four siblings - to become good students in school. In spite of their limited financial resources, all five children went to college, three to the University of Pennsylvania and two to Drexel University. I was always a very good student. I give the lion's share of credit to my mother to motivate me to become a good student.

Kenneth Durr:

Were you one of three who went to University of Pennsylvania?

William Eaton:

Yes.

Kenneth Durr:

Okay.

William Eaton:

I did an undergraduate degree in chemistry.

Kenneth Durr:

Why did you choose chemistry?

William Eaton:

Because my older sister studied chemistry, and I liked chemistry in high school. We had an excellent high school teacher. Many of the teachers at my high school, which was West Philadelphia High School, had Ph.D.s, because in the 1950s, these were people in their 40s and 50s who got their jobs when they were in their late 20s and 30s during the Depression. The only job that somebody with a Ph.D. could get would be to become a high school teacher. So, the public-school system in Philadelphia at the time was really quite good.

Kenneth Durr:

So, you got a BS in chemistry?

William Eaton:

Yes.

Kenneth Durr:

Any other focus in your undergrad?

William Eaton:

I was also very good at mathematics. As an undergraduate, I had a job working with a famous electrochemist, John O'Mara Bockris, doing calculations. I was recommended by the math department to him as somebody who was very good at calculations. He paid me a handsome sum. I was making $4 an hour in 1956 as an undergraduate, which is probably something like $40 an hour today.

There were no computers. There was a computer in the physics department, but they wouldn't let the chemists use it. I had nothing but a Friden mechanical calculator, and tables of logarithms and various kinds of functions that were necessary to do the calculations. I think I was the only student elected to the Honorary Mathematics Society who was not a math major. I was of proud of that.

Kenneth Durr:

So, you had a lot of math background. You had chemistry. Were you thinking or looking toward getting a medical degree during this period?

William Eaton:

I think I was always looking forward to getting a medical degree because I was so interested in academic achievement. The prize for an undergraduate at the University of Pennsylvania in the 1950s was to be admitted to the University of Pennsylvania Medical School, which at that time, I would argue, was the best medical school in the country. In fact, my class scored number one in the national boards over Hopkins, Harvard, and Yale. Stanford hardly existed as a significant medical school at that time.

Kenneth Durr:

So, it was just the brass ring so to speak?

William Eaton:

Yes, exactly.

Kenneth Durr:

So, did you go right into Penn Medical School after that?

William Eaton:

No, I took a year off. My two closest friends were going to Europe on Fulbright Fellowships. They basically argued with me that I was such a dull character that I should learn a little bit about life. Why not go to Europe? They told me about a new fellowship that was established when Willy Brandt, the mayor of Berlin at the time, visited the University of Pennsylvania. They established an exchange program between the two universities. I was the first Willy Brandt exchange student, called an Austauschstudent.

Kenneth Durr:

What kind of work did you do?

William Eaton:

I was supposed to study biophysics, but the only biophysics professor there was doing Stone Age science. He was basically involved in irradiating yeast with x-rays. That was something that was a popular area of biophysics because of nuclear weapons in the second world war. Before I left, I was working in the laboratory of a physicist at the University of Pennsylvania who didn't want me to go to medical school. He wanted me to get a PhD in physics. I had impressed him, I guess, in my physics courses with him.

Kenneth Durr:

Who was that?

William Eaton:

His name was Thomas Wood. He gave me a collection of textbooks to study on mechanics, electricity, and magnetism, while I was in Europe in the hope that I would then take the entrance exam for the physics department and be able to pass it by studying these textbooks. But I was so burned out from four years of working so hard to get good academic grades in order to be accepted to the medical school - I got a full scholarship - that I had no intellectual energy left when I arrived in Berlin.

The University of Berlin was called the Free University of Berlin. They were way ahead of Berkeley in the '60s. They were years ahead of the 60's revolution in this country. The Free University of Berlin had foreign ministers. The foreign ministers had meetings where they decided that the students should have greater representation at the university. In fact, at one point the students shut down the university. This was in the late '60s, early '70s. A graduate student became president of the university, what was called a rector of the university.

I learned quickly that students in Berlin didn't study and they didn't go to class. It was not necessary to go to class or to take exams for a particular course. You only had to take very general exams at the end of your student days to be eligible for some profession that you were interested in taking up.

Kenneth Durr:

So, did you spend a year there?

William Eaton:

I spent a year there. Berlin was the center of world politics. You may recall that Berlin at that time was surrounded by the Soviet Army. We had one tank regiment, 28 tanks and 1,000 troops. And the Russians had hundreds of thousands of troops and tens of thousands of tanks. It's quite amazing that my mother would let me go to this place, where the Soviets could've walked into Berlin any time they wanted. So, I actually grew up in Berlin. I was a naive, provincial boy from Philadelphia, and I became an adult in Berlin.

Kenneth Durr:

Give me, in a minute or two, this story of your run-in with the Soviets.

William Eaton:

When my two friends, who had these Fulbright Fellowships, came to visit me in Berlin, we had this idea that we should all go to visit the Soviet Union. We couldn't get any information in West Berlin about getting visas and how to travel there. So, we just walked up and knocked on the door of the Soviet Embassy in East Berlin on Unter den Linden and we were greeted at the door by a Soviet soldier, who looked shocked when he saw American passports, but escorted us in.

We waited in a room for about an hour, when a gentleman walked in who introduced himself as the cultural secretary of the embassy. His name was Leonid Dimitrijevic Mosgin. At the end of the conversation, he said, "Mr. Eaton, I hope we shall meet someday soon now that you're in Berlin for a while." I got a telephone call from him about a month later via Switzerland, because there were no telephone connections, saying he wanted to meet with me.

My roommate at that time was a fellow who was in the Army Security Agency. When he learned about meeting with Mosgin, he had an apoplectic fit and was told that I better cooperate with the counterintelligence corps. Otherwise, he may be court martialed for living with somebody who's talking to the cultural secretary, who was really the head of KGB in East Berlin. It's a long story, and I won't go into it.

I'll just say that the student who followed me, Marvin Makinen, actually did things that I would've never done, which these counterintelligence officers convinced him to do. He actually went to the Ukraine and took photographs of military installations. He was captured by the Soviets, was given a trial, was then sentenced to prison for eight years. In prison he knew that Raoul Wallenberg was still alive. There's a C&E news article about his experience.

So, I dodged a bullet by not getting too involved. A CIA agent said to me once that I wasn't a spy. I was a source. But being a source was dangerous in Berlin in those days.

Kenneth Durr:

But you got out okay?

William Eaton:

But I got out okay.

Kenneth Durr:

So, it was right into Penn Medical School at that point?

William Eaton:

It was into Penn Medical School. I'll make one last comment about this. The FBI contacted me on my first day of medical school and wanted to interview me. I had an hour-long interview and later used the Freedom of Information Act to get a transcript of the interview, which had all the details. All I got was a bunch of blackened pages except for a few comments that weren't blackened out. One was from Herbert Hoover who said that I should be watched because I may be blackmailed by the Soviet Union. The guys who interviewed me thought there was a possibility that I was gay. That would be a reason for blackmail. I do have the document saying that Herbert Hoover said that you should watch this guy.

Kenneth Durr:

Well, he -- Herbert Hoover had an opinion about you then?

William Eaton:

Yes.

Kenneth Durr:

Yeah. So, you went into medical school. It sounds like you were really oriented towards science. Tell me about how that played out as you moved through the program.

William Eaton:

When I was an undergraduate, I really enjoyed working in Bockris's research group doing calculations. I got involved in some summer research projects. The only subject that I liked in my first year of medical school was biochemistry.

I spent my first summer in medical school doing biochemical research, where I did what turned out, I learned later, to be a very important experiment. At that time, there was no evidence that ATP actually broke down when a muscle contracted, even though everybody thought ATP must be the energy source for muscle contraction. I did a rather clever experiment that won me a prize in medical school that showed ATP must have broken down, although I showed it indirectly.

What really made me very enthusiastic about research was what happened the same summer at the end of my first year when I went to the Federation Meeting in Atlantic City. I heard three speakers, Khorana, Nirenberg, and Sydney Brenner, where Nirenberg was talking about how he was going to crack the genetic code. Brenner gave this absolutely incredible, charismatic talk on how the previous speakers were just doing technician's work to try to determine the genetic code because he and his friend, Francis Crick, had already determined from genetics that it had to be a non-overlapping, degenerate triplet code. Of course, that's what turned out to be correct.

So, I wrote to Brenner and asked him if I could come to his lab the following summer. There was a letter of recommendation from one of the faculty at Penn who knew Brenner personally. Brenner sent me back this thin aerogramme, "Dear Bill, come if you like, Sydney."

I took this letter to the dean, because the medical school was going to pay all of the expenses. The dean didn't like the idea that this one line from Brenner was sufficient documentation to send me to Cambridge, England for the summer. The professor, who was actually a professor of microbiology, went to the dean and told him that of course it was a fantastic honor to be accepted by Sydney Brenner in his lab and that you would never get anything more out of Sydney Brenner because he was so anti-bureaucratic.

The dean capitulated, and I got my fellowship. I went and had this great experience - that was the main motivator for a career in research. After that experience, I knew there was no chance I'd practice medicine.

Kenneth Durr:

What kind of work did you do in Brenner's lab?

William Eaton:

In Brenner's lab, the project that I was given, which was supervised by his post-doc, Robin Munro, was to purify something, which was thought to be a protein called peptide bond synthesis factor B. I was a very obsessive-compulsive guy in the lab, and I used every protein purification method that was known to Fred Sanger, the great protein chemist in the lab, and to everybody else in the lab. I got nowhere. Brenner was very polite to me every day. I would have coffee, lunch, and tea in the afternoon with Brenner. Most days, his buddy, Francis Crick, was there. There were just a few other people who belonged to the group. Crick had no technician or postdoc. Brenner had a technician and a couple of postdocs. I was the only student.

Nobody said a word because the conversations were by these two super brilliant guys that were too intimidating for us to say anything. Had Brenner listened to me, he might've won his Noble Prize many years earlier because the enzyme that makes peptide bonds is not a protein; it's RNA. Had he listened more carefully and not maybe dismissed me as just a nice medical student trying hard but not getting anywhere, he might've thought about it a little bit.

I never said this to him directly. I've said it to other people at Cambridge, and I tried to contact Sydney on this issue a couple of years ago, but he was very ill. He died about a year ago. It has been my joke about my experience with Sydney Brenner.

Kenneth Durr:

But your work was pointing in that direction?

William Eaton:

Well, it seemed that way. It'd be really hard to document any detail.

Kenneth Durr:

So, you got into molecular spectroscopy along the way. Tell me -- tell me how you got into that.

William Eaton:

In my fourth year of medical school, I learned about the possibility of doing research towards a PhD. Whereas every other medical student was taking medical electives like neurosurgery or psychotherapy or something like that, I wanted to get started on my PhD. But it turned out that a professor of hematology named William Williams didn't like me at all. I think it was partly my personality and partly his insecurity, because the one subject that I knew well in medical school -- as I said, I become interested in biochemistry -- was biochemistry.

Many hematologists fancy themselves as biochemists. He certainly was one of them. In fact, he wrote one of the main textbooks of hematology. He was very knowledgeable in biochemistry and he was a very smart man. But I would interrupt him on rounds to ask him some difficult biochemical questions. Some of them, he couldn't answer, which embarrassed him in front of his students. He didn't like that. He obviously, then, didn't like me. So, he went to the dean who was a biochemist, not an MD. The dean at the time was Sam Gurin. He told him that the medical school should not be graduating people like me who did not have sufficient clinical experience. He basically took away my 24 weeks of elective time to start my PhD work. I spent 12 weeks taking histories and physicals at a local community hospital and 12 weeks of holding a retractor for surgeons in the operating room or sewing up knife wounds in the emergency room.

At any rate, it all turned out well because when I graduated, I was one of the first recipients of a fellowship from the Pennsylvania Plan to Develop Scientists in Medical Research, which was incredibly lucrative. It was a $10,000 a year tax-free fellowship in 1964, with no taxes and a $1,000 increase every year. So, I had this fantastic graduate fellowship and I could do what I wanted. I was always enamored with thermodynamics and had worked in the laboratory of a British scientist named Phillip George, who was this brilliant biophysical chemist. My plan was to do my PhD thesis with George.

I started in June of 1964 to work in his laboratory. In that laboratory was an assistant professor named Alan Adler. Alan Adler was very friendly with a new associate professor of chemistry in the university named Robin Hochstrasser, who was a molecular spectroscopist. Alan Adler also had another friend named Joseph J. Higgins. Joe was a theorist who worked primarily in statistical mechanics.

Adler was a thermodynamics fanatic. Hochstrasser, the spectroscopist, loved quantum mechanics. Joe Higgins's love was statistical mechanics. These are the three branches of physics. These guys met every day at the Deck Bar at 34th and Walnut Street to discuss science. They argued about which was the most important and most superior branch of theoretical physics -- one, quantum mechanics, one, statistical mechanics, and one, thermodynamics. They allowed me to listen in on their conversations. If we didn't meet before dinner, we would meet after dinner. One night, we went almost until midnight when Robin Hochstrasser wanted to know what I did. I told him about the fact that I was doing thermodynamics with Phillip George. He thought that was ridiculous. "That this was a stupid thing to do. You should think about something like spectroscopy."

Then he asked me about what molecule I was working on, and I told him I was working on cytochrome c, and that I actually had a gorgeous crystal of cytochrome c. When he heard that, he jumped because his favorite form of molecular spectroscopy was to look at the spectra of single crystals of organic molecules. I had this gigantic single crystal of a protein molecule and this protein molecule contained hemes, which are iron porphyrins. One of his interests in molecular spectroscopy was porphyrins. So, he had a great interest in looking at these crystals.

So, at midnight, we went to his laboratory, and he sealed my crystal onto the stage of a polarizing microscope, turned the microscope towards a spectrometer and used the light source of the microscope. The light shined through this crystal and was focused through the slit of the spectrometer. He took a spectrum in two different polarizations of plain polarized light, went into the darkroom, developed the film, came out, and said, "We've made a discovery." I said, "What's that?" "We've discovered that this band that you're interested in at 695 nanometers, which you told me was a conformationally sensitive band, is z-polarized, that is perpendicular to the heme plate. This is a discovery." I didn't know what he was talking about. I didn't know what z polarization meant. He then explained that this was the direction of the transition moment. I didn't know what transition moment meant.

Two weeks later, I followed him to an international meeting in biophysics where he wowed me like Sydney Brenner wowed me in Atlantic City. This charismatic guy gave a fabulous 10-minute talk about the result, which he attributed to me. I had nothing to do with it except that I handed him the crystal. He convinced me to come to his laboratory, that I could do a great PhD thesis on single-crystal spectroscopy of heme proteins, which I did. That was my thesis.

Kenneth Durr:

So, no more thermodynamics?

William Eaton:

No more thermodynamics.

Kenneth Durr:

How long did you work with Hochstrasser?

William Eaton:

I actually worked with him for, I guess, just about two years. I started in 1966. At the end of 1967, I got a draft notice. I had to finish my PhD thesis, so I went to the draft office and spoke with a mean-spirited bureaucrat. I told her, "You can't possibly draft me." I should've said earlier that Gurin had advised me not to take an internship because if I took an internship, I would be drafted. If I didn't take an internship, I was not a qualified physician and, therefore, I wouldn't be drafted. So, if I wanted to get a PhD, just go right for the PhD and forget internship.

Kenneth Durr:

But it didn't work out that way?

William Eaton:

It didn't work out that way because the mean-spirited bureaucrat said to me, "Dr. Eaton, do you have a degree of doctor of medicine?" I said, "Yes, I do, but I'm a scientist. I'm not a physician." She said, "Look at this line, Dr. Eaton," and she showed me in this book that I was subject to the doctor draft because I had a Doctor of Medicine. I didn't know what to do at that point. But then she told me that I should think about joining the U.S. Public Health Service. I didn't know what the Public Health Service was. She said, "they have an office at Front Street in Philadelphia. Why don't you go visit there?" So, I went the Front Street in Philadelphia. It's called Front Street because it's right next to the river.

There was an Office of the U.S. Public Health Service, where there were these two guys, sloppily dressed in what looked like naval uniforms. They really looked like they hadn't pressed their shirts in weeks. Their job was to make sure that people who came off the ships didn't have smallpox or any other severe infectious disease. Philadelphia at that time was a major seaport. It is no longer.

They told me about the Public Health Service and that I could get in, but I would have to pass an exam. They gave me an exam, which I just barely passed because it was all about tropical diseases like schistosomiasis and all these names that I had totally flushed out of my brain. In any event, I qualified as an officer in the Public Health Service.

Now the problem was to find a job. They told me that the National Institutes of Health was actually part of the Public Health Service. I had been to the National Institutes of Health to do some calorimetry many years earlier with Phillip George when I was doing thermodynamics, so I asked him whether he had any contacts there, and he did. His one contact was Gary Felsenfeld. He called Gary Felsenfeld, but Gary had changed his interest from quantum mechanics, which he did with Linus Pauling, to molecular biology. He said that there was a more suitable advisor for me named Elliot Charney in the laboratory next door, in Building 2 at the NIH. So, I contacted him, and he invited me for an interview and very happily accepted me as a post-doc. That's how I came to the NIH on January 15th, 1968.

Kenneth Durr:

And what kind of reputation did NIH have in the 1970s?

William Eaton:

Well, my fellow graduate students thought this was a disaster. They had never heard of the National Institutes of Health. I was doing my PhD in a solid-state physics building. As a group of chemical physicists, they just knew that it was a federal research laboratory. Therefore, it must be mediocre, as all federal institution research laboratories were thought to be at the time except for a very few. They felt sorry for me. They thought that after a PhD with Hochstrasser that I would be going on to do a post-doc with a famous spectroscopist at a major university, but it didn't turn out to be that way. But of course, it turned out to be the luckiest break of my life.

Kenneth Durr:

Tell me -- give me a sense of your impression of this lab, Elliot Charney's lab, at that point when you came in.

William Eaton:

There were some smart people there. But overall, I would say it was rather a moribund laboratory. Elliot himself was a really smart man. Edwin Becker, who was the chief of the laboratory, was also a very smart man. There was one other guy who was quite controversial, William Hagins, who got elected to the National Academy who was also very smart. But I would say the rest of the scientists were from mediocre to good, not even very good. Let me just think for a second. There were a couple of physiologists, one of them whose name I can't recall, and there was also another vibrational spectroscopist, Ira Levin, -- I would say Ira was really very good.

Kenneth Durr:

This is the Laboratory of Chemical Physics.

William Eaton:

It was at that time called the Laboratory of Physical Biology. It split in 1972 when Edwin -- we called him Ted -- Becker became the head of the Laboratory of Chemical Physics and Elliot Charney became head of a section and I was in his section. Then in 1972, I was offered a permanent position. I was told the same thing in 1970, but then I dismissed it because I didn't think this was such a great place to be.

I was very strongly influenced by a discussion with Martin Gellert, this super smart guy that you're going to be interviewing soon, who was a very close friend of Elliot Charney. I remember him telling me that, "I thought you liked the life of pure research from your experience with Sydney Brenner at the Medical Research Council Laboratory of Molecular Biology in Cambridge. So, why are you interested in going to a university? This is the best place in the United States to do research."

That changed my mind. I did look a little bit for jobs at universities. One of the reasons I talked to Gellert was it was actually a major recession. You may recall in 1970 in the U.S., universities were not hiring anybody and that's what caused my depression. This conversation with Gellert did have a big effect on me. When I was offered the job again in 1972, I did not dismiss it, which was pretty insulting to the scientific director, when I was offered a job in 1970. Because of limits on FTEs at the time, full-time equivalents, I had to wait for a couple of years. In 1970, I had my two years as a public health center officer, so that satisfied my military obligation. It was in 1973 or '74 that I actually got my permanent civil service position. I joined the Public Health Service again because at the time medical officers were making much more than civil servants. So, I went back into the Public Health Service and became a Commander in the Public Health Service.

Kenneth Durr:

Had you started working on sickle cell by the early '70s at this point?

William Eaton:

I started in 1972, and that was motivated by a visit from a post-doc in Cyrus Levinthal's lab. He was a famous computer scientist at Columbia; the post-doc's name was Shoshana Wodak. She told me about a paper that was going to be published by Max Perutz and the electron microscopist at Cambridge, John Finch, on the structure of the sickle cell fiber. I had just started making measurements on single sickle cells because this was the beginning of widespread interest among scientists and hematologists in sickle cell disease. This was, I forget the name of the act, but I think it was called the Sickle Cell Disease Act or something that established the Sickle Cell Division in the Heart Institute.

It seemed like a natural for me because sickled cells were very much like single crystals of heme proteins. I had been working on single crystals of hemoglobin. The cells contained oriented fibers of the mutant hemoglobin, sickle hemoglobin. So, I made these measurements and determined the relative orientation of the hemoglobin molecule in the fiber.

Kenneth Durr:

Had anyone done that kind of work before?

William Eaton:

It turned out that Makio Murayama was another motivating factor because he actually got the wrong answer. He thought the heme planes were actually parallel to the fiber axis. We determined in these measurements with Jim Hofrichter, who was a postdoc at the time, that they're actually perpendicular to the fiber axis. We wanted to know how this fit into this Finch-Perutz structure. We went to Richard Feldman, who was one of the pioneers in molecular graphics in the computer division and we saw for the first time three-dimensional pictures of the hemoglobin molecule.

We realized from the structure of the hemoglobin molecule that the Finch-Perutz molecule model for the sickle fiber couldn't possibly be correct because they had the site of the mutation pointing into the solvent. So, it made no sense at all. How could that residue on the surface of the molecule pointing into the solvent make the molecule aggregate if it wasn't involved in a contact in the fiber? That would mean that the fiber contacts were all normal residues. So, I wrote a letter to Max Perutz in Cambridge. I don't know whether he remembered me from when I met him a couple of times when I was there in 1962, 10 years earlier. He wrote me back a letter saying, "Please come to my meeting in London" - what historically was one of the most famous meetings on hemoglobin held at the Royal Society in London - "on hemoglobin to tell me about your research."

My research was to show that he had made what really was a blunder. He also said, "Of course, I'll pay all of your expenses." How many scientists today would invite somebody to this big international meeting to show that they were wrong and that they had actually made a blunder? I went to the meeting and was given only two minutes to make my presentation because I was not invited. The chair of the session didn't have me on the program. There was 15 minutes that was supposed to be shared between me and Stuart Edelstein, who had a structure for the fiber that was different from the Finch-Perutz structure, which turned out to be the correct structure. I always kid him that he took 13 of the 15 minutes.

I had a bunch of slides, but I had prepared for this. I was telling myself the night before, what am I going to do if they only let me show one slide? So, I actually prepared a single slide and was able to make my point with this single slide. That seemed to impress some of the people in the audience, who encouraged me about what I was doing. So, when I came back to the NIH, I convinced my colleague, Jim Hofrichter, who was actually hired as a postdoc with Elliot Charney to continue to work with me. Elliot was an incredibly generous guy. He said to Jim, "Look, this stuff with Bill Eaton is much more interesting than what you could do with me, so you should spend your time working with him." This was what a fabulous person Elliot Charney was.

Kenneth Durr:

What was Hofrichter's focus? Was it different from yours?

William Eaton:

No, he basically had a physical chemistry background. Also, he had done some elegant work on circular dichroism spectroscopy. So, he knew a lot about spectroscopic instrumentation. The work I did on the sickle fiber was done on a microspectrophotometer similar to the one I had built in Robin Hochstrasser's lab. He made some nice technical improvements to the microspectrophotometer that we used for the sickle cells. We used the same microspectrophotometer to watch the formation of the sickle hemoglobin fibers by looking at the birefringence. I did the hemoglobin purification. Together, we studied the kinetics.

That's when we discovered this delay period prior to fiber formation and also discovered its enormous temperature and concentration dependence. Phil Ross from the neighboring Laboratory Molecular Biology joined us. He was an expert in calorimetry. He showed that the delay that we observed by optical birefringence was identical to the delay that he saw in his scanning calorimeter, which really convinced us that we were watching fiber formation and not just the later orientation of the fibers. Maybe the fibers formed, but it took a while for them to align to give birefringence.

We published this paper in 1974 on the kinetics of hemoglobin S. It was called gelation because when the fibers form, they make the hemoglobin solution viscous, like a gel. We called it a new understanding of the pathophysiology of sickle cell disease. That was when we really took off and spent the next six years, full-time, working on sickle cell disease.

Kenneth Durr:

Did you realize right up front the importance of --

William Eaton:

That was where my medical background came into play. What I realized was that because of this delay time, it was quite probable that most cells, rather than sickling inside the narrow vessels of the tissues, actually could escape the vessels before the fibers formed and that this enormous sensitivity of the sickle cells could account for many of the features of the disease. For example, the episodic nature of sickle cell crises -- sickle cell crises are totally unpredictable, but they seem to be triggered by things like fever or an infection. Fever, because of this huge activation energy, shortens this delay period and increases the probability that the cell would actually sickle inside the capillaries.

It all seemed to form a coherent picture that could explain an enormous amount of the clinical information about sickle cell disease with a simple postulate that clinical severity is determined by the relative time of sickling to the time it takes for a cell to get through the microcirculation. So, anything that increases this transit time or decreases the sickling time is bad and makes somebody sicker. Something which shortens the transit time and increases the delay time is actually positive. It's really a simple and I think powerful statement that has held up until today. It took a long time for hematologists to accept this, but it's now well-accepted by the hematology community.

One of the reasons was, unfortunately I had a colleague, Alan Schechter, who for reasons which I've never quite understood, argued against it and published many articles in hematology journals with and alternative hypothesis that what's important are the equilibrium aspects. not the kinetics. That's since been dismissed by just about everybody, possibly even Alan, but I'm not sure.

Kenneth Durr:

But he didn't have the kind of training that you had to look at the kinetics on it?

William Eaton:

No, he didn't have any background in physical chemistry. He was a very, very smart man, and he did know a lot of biochemistry. He didn't have a PhD. He just had a medical degree. So, I think that was part of the reason.

Kenneth Durr:

Talk about how your research in sickle cell progressed. You kept with it for quite a few years after --

William Eaton:

I stayed with it full time until 1980. Then I became interested in conformational dynamics of proteins. Jim Hofrichter had built this fantastic time-resolved instrument for looking at the kinetics of conformational changes in hemoglobin following photodissociation of the carbon monoxide complex. This was very much related to the question of the mechanism of cooperative oxygen binding by hemoglobin, the so-called allosteric mechanism of Monod, Wyman, and Changeux. Eric Henry came to the lab as a postdoc in 1980, and he developed this very powerful method for analyzing the data based on a mathematical method called singular value decomposition, which is now widely used in the scientific community. He didn't invent the mathematical method itself, but he developed it as a practical application for looking at chemical kinetics.

The three of us published several papers during the 1980s on this. At the same time, I became interested in the equilibrium properties of binding oxygen to hemoglobin. This is very different than sickle hemoglobin kinetics, where the equilibrium properties are not that important. But in the case of oxygen binding itself, it turned out from the first measurements in 1905 of the cooperative oxygen binding of hemoglobin, which was an equilibrium measurement, that you could understand the physiological significance of the cooperative binding curve. So, for the past over 100 years there's been an enormous amount of work on trying to understand oxygen binding to hemoglobin.

The first theory was actually invented by Linus Pauling. That then became known as the sequential model, further developed by Koshland, Némethy and Filmer. The next theory was developed by Monod, Wyman, and Changeux, called the allosteric theory, in which this brilliant French geneticist, Jacques Monod, understood enough statistical mechanics to develop an elegant theory for how hemoglobin binds oxygen cooperatively based, in part, on an observation of Max Perutz that hemoglobin just has two confirmations. Rather than binding an oxygen molecule to one subunit (hemoglobin has four subunits), that affects the affinity of the neighbor, which was Pauling's idea, binding increases the probability that the molecule will make a transition from a low affinity structure to a high affinity structure. So, the cooperative oxygen binding occurs from Le Chatleier's Principle, that as more oxygen molecules bind the equilibrium shifts towards the higher affinity state. That ends up giving the sigmoid curve.

Kenneth Durr:

So, were you testing this Monod theory --

[talking simultaneously]

William Eaton:

We were testing this Monod theory by kinetics. The critical test came with experiments of Andrea Mozzarelli, who did the key experiment on sickle cell hemoglobin in the lab; his experiments were on actual sickle cells. His experiments showed that it is very likely that the vast majority of cells escape the microcirculation before sickling begins. We had just had speculated this based on physical chemistry of purified hemoglobin solutions. He actually demonstrated this in sickle cells.

When he went back to Parma, his supervisor, Gian Luigi Rossi managed to get enough money, which was, at that time $100,000, to buy a Zeiss microspectrophotometer. This is a gorgeous commercial microspectrophotometer, where we were able to measure, well, actually they measured, oxygen binding to sickle hemoglobin crystals, which were known to be in the T quaternary structures. The T quaternary structure was what the argument was all about for many decades. We showed that structure binds oxygen perfectly noncooperatively. It was the confirmation of the Monod model.

We sent the paper to Nature. It was rejected. I couldn't understand how they could reject this paper. It was rejected by Max Perutz, who's played a big role, as his name comes up over and over again in my life. I wrote a letter to Perutz telling him that, by the way, this paper also showed that your theory of the Bohr effect must be correct. That was his favorite result from his X-ray structure, which was to show that the intersubunit salt bridges are responsible for the Bohr effect.

We did this measurement, which by X-ray crystallography showed that the salt bridges did not break when oxygen bound to the hemoglobin in the crystal. What we discovered was that the oxygen-binding curve was totally insensitive to the pH, which was part of our paper. Perutz then called Nature and said, "Accept the paper." They accepted the paper.

Kenneth Durr:

There was some self-interest in it.

William Eaton:

Yes.

[laughter]

Kenneth Durr:

That's great. Well, let's shift gears just a little bit. We talked a little about the administrative side and how a lot of it's set up and some of the changes that were going on. And you talked about splitting off the laboratory of chemical biology into --

William Eaton:

Physical biology, it's called the --

[talking simultaneously]

Right.

Kenneth Durr:

-- into two groups. Why was that -- how did that work out?

William Eaton:

I think that worked out well. The physiologists went to this new institute, which was called at that time the National Institute of Arthritis and what was it -- I'm trying to think of the full name. I think it was called National Institute of Arthritis and Muscular Skeletal Diseases, NIAMS. We stayed in our institute, the National Institute of Metabolism and Digestive Diseases and eventually the National Institute of Diabetes and Digestive and Kidney Diseases. Correct me if I'm wrong.

Kenneth Durr:

Right.

William Eaton:

The next incident in my career, which had an influence on the structure of the lab, was that I gave a lecture about our sickle cell work, the discovery of this delayed time with its enormous concentration dependence, which I didn't mention earlier was the 30th power. It depends on the 30th power. That is the highest power, or the highest sensitivity, of any concentration dependence of any process in all of science today. Nobody's found anything that comes even close to that.

In any event, Wally Gilbert, the famous scientist at Harvard, was at this Gordon Conference when I presented my work. He invited me to give a lecture at Harvard and John Hopfield, the famous biophysicist at Princeton, invited me to give a lecture on this at Princeton. In consecutive weeks, I went to Princeton and Harvard to talk about this work. There is an amusing anecdote about the difference between Harvard and Princeton. At Princeton, John Hopfield introduced me by saying that I did my undergraduate degree at the University of Pennsylvania. I then did my medical degree at the University of Pennsylvania. “And then he even stayed to do a PhD at the University of Pennsylvania” when the audience laughed. Then he said, "And now, he's at the NIH where he's a commander in the U.S. Public Health Service." Stony, reverent, silence.

I guess you can see what's coming. At Harvard, Wally Gilbert introduced me as “our speaker today is Bill Eaton from the National Institutes of Health. He did his undergraduate degree at the University of Pennsylvania. He got both a medical degree and a PhD at the University of Pennsylvania.” No response from the audience. ”Now he's a commander in the U.S. Public Health Service.” They all laughed. The entire audience laughed because I was a Commander in the U.S. Public Health Service.

Kenneth Durr:

This doesn't fit in to expectations.

William Eaton:

Then he was involved in talking to Martin Karplus to invite me to Harvard to be a Visiting Professor for a semester. I taught a course in physical chemistry with Steve Harrison, who was a crystallographer. He is still at Harvard, but now at Harvard Medical School.

Kenneth Durr:

When was the Harvard --

William Eaton:

This was 1976. Steve taught structural biology and statistical mechanics. I taught kinetics and elementary quantum mechanics. That's how we divided the course. At the end of the semester I gave, what probably was one of my best seminars ever, to the physical chemists at Harvard about my work on sickle cell disease, a more refined version of what I'd given them a couple of years earlier. These two lectures that I told you about were in 1974.

In any event, I happened to give a really, really good lecture. Several months later, I got a call from the head of the biophysics graduate group, Arthur Solomon. Before that, Martin Karplus asked me whether I was interested in becoming a professor at Harvard in the Chemistry Department, and I didn't think anything was going to come of it. But then Arthur Solomon called me and said that the graduate group in biophysics had met. The graduate group consisted of professors from every science department. There was biology, applied physics, chemistry, molecular biology, biochemistry, with a representative from each of the main science departments that had some interest in biophysics. He said that I was the unanimous selection to become the new head to replace him, as he was retiring as head of biophysics. It came with a full professorship in the chemistry department, because you had to have a professorship in an actual department to become head of the graduate group, and that the physical chemists had selected me.

He asked me whether I was interested. I said, "Well, let me think about it." Even before I had time to think about it, the next day he called me to tell me that he had to withdraw the offer because the organic chemists discovered that the physical chemists were offering me a professorship in the chemistry department without consulting them and that the organic chemists wanted to interview me. In February 1977, I went for an interview. The interview was a total disaster. It was a combination of things, but it was held in the new Biolabs building at Harvard at 4:00 p.m. I never gave the lecture because the bulb in the projector burned out; there were these famous physical chemists in the audience; they didn't have a bulb, and they didn't know where a bulb was because it was in the Biolabs. They sent a graduate student to find a bulb. He never came back.

I said, “Okay, I'll use transparencies. I won't be able to show you the raw data, but I'll just have to draw it on transparencies, but I'll need a transparency projector and a screen.” There was a screen, but there was no transparency projector. 15 minutes later, somebody came back and said they couldn't find a transparency projector. Now, it's after 4:30 p.m., or even later than that, and I said that, well, “I'll give it on a blackboard” because all my lectures, which went over extremely well, were done on a blackboard. So, I became pretty good at giving lectures on a blackboard. They said there's no blackboard, but there's a whiteboard. I said, well, okay, I'll use the whiteboard if somebody can just give me something to draw. I said “where's the switch for the whiteboard?” Somebody pointed me to the switch to lift the screen to get to the whiteboard. The screen didn't lift. So, no whiteboard, no transparency. There was no such thing as a PowerPoint presentation. And no slides.

It was quarter-of-five by this point, and there was a lot of noise in the audience. Why? Because there was one of the big biology courses scheduled at 5: 00 p.m. and the students came marching in. The undergraduates didn't give a damn that there was a seminar going on, so I basically got up and walked out.

My final appointment that day was with Frank Westheimer, who I think was the guy who insisted that I come back for an interview. I had interviewed earlier in the day with several people who basically assumed that it was a done deal, and they were trying to impress me with how great it would be to be a professor at Harvard. I sat for an hour in Westheimer's office. I was totally, emotionally destroyed, I think, by this experience of coming for an interview and having no seminar at all.

Westheimer went on and on about his research. I hardly looked up. I might have smiled. I never asked him a single question, so I'm sure Westheimer must have thought: who's this smart guy who wants to be a professor in my department, and he can't even ask me a single question? I don't even think I said something like, "Oh, that's interesting." I just sat there and looked at him. I never heard from Harvard again.

I've never heard from them, not even to say we're sorry that things went so badly, and that you weren't able to give your seminar, but blah, blah, blah. I think that their wanting me to be the head of biophysics at Harvard motivated me to build a biophysics department here at the NIH. It made me work very hard to build up the Laboratory of Chemical Physics.

The first move was 1981. Martin Karplus called me and said that one of the smartest, or perhaps the smartest graduate student he ever knew at Harvard, who was his graduate student, Attila Szabo, didn't get tenured in Indiana, so I should hire him. I said, "That's a good enough recommendation." But we had no room to put him. Gary Felsenfeld kindly gave up his cages that he had, where he was keeping chickens in the building. I think they were chickens. I could be wrong, but I think they were chickens. There was no big animal facility at the NIH then and people had to worry about their own animals We built an office for Attila. Then Ted Becker got the job as Director of the Office of Research Services.

[inaudible commentary]

Kenneth Durr:

So, we were talking about building up your lab.

William Eaton:

Right.

Kenneth Durr:

And you just hired Attila Szabo.

William Eaton:

Right, and that turned out to be a fabulous hire. He's now considered one of the top theorists in the country. He was elected to the National Academy several years ago. He's been key in helping to build the lab because he has this fabulous personality, and he's an incredibly smart guy.

The next was in 1983. In 1983, Ted Becker had retired from the lab, so after his retirement, we had a rotating lab chief system for a few years. I was the second lab chief after Bill Hagins. Ted Becker wanted to hire a former post doc of his to take over his NMR facility. I knew the person he was talking about -- her name was Gitte Vold; she was actually a good friend of mine. I liked her very much, but said to Ted said, "Wait a second. This is an opportunity to get a really top-notch person." It may be the first time anybody at the NIH ever did an international search. I'm not sure of that.

In any event, we did an international search. Our two top candidates were Geoffrey Bodenhausen and a young man named Adriaan Bax. We interviewed these two guys. We first interviewed Bodenhausen, who was also a friend of Ted Becker, and this kid Adriaan Bax, who was 26 years old at the time. They both gave seminars, but the Bax seminar was spectacular, not because I understood what he said, but what I did understand was that this guy knew what he was talking about.

Of course, he subsequently became one of the world leaders in NMR. He had other offers, and I had to figure out some way of getting him here. Ted Becker became a great help because he taught at Georgetown University for many years as an adjunct professor, and he used his influence in the following way. I learned that Ad Bax had a German girlfriend, Ingrid Pufahl. I knew he had this very romantic relation with her, and it was obvious that this was somebody he wanted to be with. So, I thought that we could out-compete any other place if I could get her a fellowship at Georgetown University, which Ted Becker arranged. She actually got a graduate fellowship in sociolingustics. It's not like science where everybody gets a graduate fellowship.. It's in the humanities where it's very hard to get a full scholarship. Ted arranged that, and that was possibly what turned the tide in favor of the NIH.

Ad came in 1983. In 1986, I was made the permanent lab chief.

Kenneth Durr:

That's when the rotating stopped?

William Eaton:

The rotation stopped, and I was appointed the permanent lab chief. The next hire turned out to be Marius Clore and Angela Gronenborn. Ad had learned about this new method in NMR for solving the structure of proteins in solution, the three-dimensional structures of proteins in solution, which was first done in a laboratory of a man named Kurt Wüthrich, who won the Nobel Prize later for this; he said that he knew of people, this young guy Marius Clore, who was married to Angela Gronenborn, a biochemist, that knew how to solve these structures and maybe we could hire them.

Kenneth Durr:

Where were they from?

William Eaton:

They were directors at a Max Planck Institute in Munich. The reason that we thought we could hire them was Jim Wyngaarden asked Ed Rall to find a scientist who could take over a new program, which ultimately got the name Intramural AIDS Targeted Antiviral Program, who didn't have a vested interest that could profit himself by this new Congressional authorization to do structural biology research on HIV.

I was selected by Wyngaarden at the advice of Ed Rall to run the Intramural Program. The funding that Congress had legislated was split 50-50 between Intramural and Extramural. It is usually 10-90, but in this case it was 50-50. That money was used to build infrastructure in structural biology. This new method was available, where you could solve the structure of proteins in solution and you didn't have to crystallize them. So, I thought this was a great idea and we would go after Clore and Gronenborn.

I remember having to present this idea of using this money to the NIH Council. I never forgot this embarrassing situation where this guy Michael Rossmann, who was this famous structural biologist who solved the structure of viruses, made a comment after my getting primed by Ad Bax on what to say. I told them that there was a new method to solve the structure of the three-dimensional structures in protein solution by nuclear magnetic resonance. Rossmann told Wyngaarden: don't believe anything that I said; “he's talking nonsense, it's impossible to solve structures by NMR. It can only be done by X-ray crystallography.”

After the meeting, I met with Wyngaarden and told him that Rossmann had to be wrong because this guy Bax knew what he was talking about. We did get the money to do this, and we brought Clore and Gronenborn here. They went on to solve more structures of HIV than any other group in the world. Gronenborn prepared the proteins and Clore solved the structures and analyzed the data. So, it was mainly due to Marius Clore. There was a period in the early '90s where he had solved more NMR structures of proteins by himself than the rest of the world combined. He's quite an amazing scientist. He also got elected to the National Academy later, as did his wife, Angela. They separated around the year 2000; they got divorced, and Angela's gone on to have a very successful career herself. She was actually elected to the National Academy before Marius, but that's because the National Academy, of course, had this very strong bias towards women. In any event, that's a totally separate issue.

With Bax, Clore, Gronenborn, and Szabo helping me recruit people, we went after an experimentalist. The idea of recruiting, which I still maintain today, was not to worry about the subject matter - when we hired Ad Bax he didn't know what an amino acid was. He really didn't. He couldn't tell you the structure of the simplest amino acid. The best candidate we had was yet another NMR spectroscopist. At a university this would never happen. The university would say, "No, no, we have many." But I learned -- when I asked Max Perutz, not when I was there in 1962, but later when I got to know him quite well. He would visit the NIH, and I would always talk to him. I asked him how he built this laboratory. When I was there in 1962, he had hired six group leaders, and they won six Nobel Prizes. Sanger won two, Huxley didn't win one. So, it was Kendrew, Perutz, Crick, Sanger, did I mention Brenner? Brenner, Crick, Perutz, Sanger and Sanger, okay. Sanger won two, so that's the six.

He said what you do is “hire the smartest scientist you can and let them do what they want.” That's been actually a great characteristic of NIDDK; we're judged on what we accomplish. I think every PI that I know does what he wants to do, and there's no direction from the Scientific Director – “you shouldn't do this, you should do that”. The Scientific Director may give advice that maybe you should pursue this because this is more interesting, or you're doing better at this than the other, but not because this is more relevant to kidney disease, or diabetes, or digestive diseases

In fact, I can't cite exactly where to find this, but I remember reading many years ago that our institute was, I think, the only institute at the NIH where the mission of the institute was to do basic research. Whereas, the mission of every other institute is directed toward the name of the institute. I don't know whether it's still, maybe Nicole Ray knows, is it still in our mission? I don't know.

Kenneth Durr:

So, how many -- you were taking me through the list of people you brought in. How many in National Academy fellows have you had?

William Eaton:

Robert Tycko was followed by Gerhard Hummer, then Phil Anfinrud, then Robert Best, and then Hoi Sung Chung. Right now, there are eight PIs in the laboratory. There were two National Academy members, Angela, who left, and Robert Zwanzig, one of the most famous theorists of the 20th Century, also came to our lab. He's a legendary theorist in statistical mechanics, but he enjoyed talking to Attila so much that he left the University of Maryland. Zwanzig actually spent one-third of his career at the NIH. He spent one-third at the National Bureau of Standards, one-third at the University of Maryland, and one-third at the NIH.

Right now, in the National Academy there's I , Attila Szabo, Ad Bax, Marius Clore, and definitely within the next few years, Robert Tycko. I guess I was counting myself as I hired myself.

[laughter]

William Eaton:

There will soon be five out of the eight people in the laboratory. Robert Best is an excellent candidate, even though he's only 43. The average age now is over 60. The National Academy of Sciences is looking very hard for younger people because it's become sort of an old fogey's organization. Robert Best, at age 43, is arguably the top computational biophysicist in his generation or in his age group. So, I have very high hopes that he'll get elected within the next few years. I'm sure Rob Tycko will be elected because I know from the balloting that he's going to get elected. I can't tell you exactly when, whether it's this year, or the next year, but he is going to be elected. He's that high up on the ballot.

Kenneth Durr:

Well, let's step back and talk a little more about your work because we haven't even gotten to protein folding yet. And that occupied a good bit of your time.

William Eaton:

Yeah, it did. Actually, it was 25 years of my research career. That started with a conversation with a well-known theorist, Peter Wolynes, at a meeting in Moscow when he said “why don't you start working on a hard problem.” I was at that time just working on hemoglobin and allostery, and he told me about protein folding. He said that because of our nanosecond time-resolved instrument, we had the capability of doing kinetics on time scales that are not accessible to the biochemists who work on protein folding. I said, "All right, send me the ten best papers on protein folding, and I'll look at them." The big review was by Buzz Baldwin, at Stanford, with Peter Kim. My problem was that I kept falling asleep reading the article. I said, "I don't know. This is not all that interesting to me." But then a biochemist at Penn that I knew, Heiner Roder, gave a seminar. He told me about an experiment that they had tried in Robin Hochstrasser's lab to fold cytochrome c with a laser pulse, but it didn't work. I realized that we had a better instrument, and we could make it work, and we did. It did work. We saw the early events in the folding of cytochrome c, and that started what came to be known as the fast folding field. We were now working on time scales that were accessible to computer simulations, and that was part of the motivation, a major motivation.

There was a meeting in Puerto Rico that I was invited to, along with other people doing time-resolved spectroscopy. They said we want you guys to work on protein folding because our molecular dynamic simulations can be done out to about 10 nanoseconds, and they're going to be longer in the future, so we need experiments that will overlap with our time scales. That's why we need people doing very fast folding experiments. We realized, as did several other groups, that the best technique was temperature jump with a laser, where you just heat the solution with a laser. That led to the most important studies probably during that period of time, where we did experiments on an alpha helix and, probably the most important one, on a beta hairpin. A beta hairpin is a little object of just a polypeptide chain that turns into the shape of a hairpin, but it turned out that this beta hairpin had all the properties of a small protein. That became the benchmark for every simulation group in the world to actually simulate our experimental results. What we discovered was that it behaved like a simple two-state system, and we measured all of the kinetics and characterized it. We built a statistical mechanical model to explain the results, which then led to a very simple statistical mechanical model for a whole protein. It remains today probably the only theoretical model that can explain the widest range of properties that people observe in protein folding - all of the equilibrium properties and all of the kinetic properties. It's a simple model. Some people call it the Hueckel model of protein folding, like the Hueckel model of molecular orbital theory. It also has become very popular.

Then in the early 2000s, -- it was actually in the late '90s - I went to an American Chemical Society meeting and saw a poster on single molecule spectroscopy. I realized that it may be possible to watch a single molecule fold. So, I decided, like several other groups, to build a single molecule instrument to watch proteins fold, one at a time. I hired a very smart post doc, Eric Lipman, from Berkeley, who was an experimental astrophysicist, and I told him that “you've been looking at radiation from a single star, I want you to look at the light coming from a single molecule.” He became intrigued and built a state-of-the-art instrument. We published a very highly cited paper in Nature, with another smart post doc that I had, Benjamin Schuler, on single molecule protein folding.

This work evolved until Hoi Sung Chung, who's now a principal investigator in the lab, came to the laboratory and realized that we could actually measure the time it took, not for a protein to fold, but for a protein to actually cross the free energy barrier. What happens is a protein sits and waits until it gets enough thermal energy to cross the free energy barriers. The rate coefficient, the rate at which a protein folds, depends on the waiting time before it actually crosses this barrier. But the time that it crosses this barrier is this very rare event that has a very short time. It was predicted by a computer scientist many years ago for IBM, who said if we could ever watch a protein fold by molecular dynamics, it would be very boring because the protein would just move around and then suddenly it would cross the barrier and fold. That's the event we were looking for.

Attila Szabo had developed a theory on the time, the average time that it would take for a protein to fold. What we measured came extremely close to his theoretical prediction. That was my last big contribution to the protein folding field. It's become a very popular area of current investigations by physically oriented scientists. A lot of physicists are involved. They're doing it by optical tweezers, and by fluorescence. I dropped the whole field about three years ago, mainly because of a comment that was made to me 10 years earlier by a molecular biologist, Dan Camerini-Otero, who was a student of Gary Felsenfeld. You can see that Gary's name comes up several times.

Kenneth Durr:

Almost as much as Max Perutz.

William Eaton:

[laughs] Right. I don't think Gary would say that he had much of an influence on my career; although, he did. He was very helpful in getting me elected to the National Academy of Sciences. He was a major factor.

His former post doc, Dan Camerini, had gone to a meeting that Frances Collins had organized on sickle cell disease. At that time there was only one drug, hydroxyurea, for sickle cell disease. After the meeting, Camerini said, "You should get back into sickle cell disease research. There's only one drug and it only helps about half the people. You should be able to develop an assay or do something in this area. So, why don't you do it?" I said okay.

I hired a super smart graduate student, who was a post doc with me for one year, named Jeffrey Smith. The deal with Jeffrey was very interesting. Jeffrey was part of the Cambridge-NIH partnership. His PhD supervisor was Chris Dobson. Dobson asked me if I could take over as Jeffrey's supervisor because you have to have both an NIH supervisor and a Cambridge supervisor. Jeffrey was so much smarter than his NIH supervisor that he said, "I can't work with this guy any longer."

Jeffrey went to the University of Pennsylvania, which made me feel a little more affectionate to him, where he got an undergraduate degree in biomedical engineering. He also got an undergraduate degree in economics from the Wharton School. He also got a master's degree in bioengineering and a master's degree from the Wharton School. He did two four-year programs, one two-year program, and the Wharton School program, which is a full-time two-year program, for a Master's in Business Administration. He got all four degrees in four years and one summer, and he got an A in every subject, except in one he got a B plus. When asked by Attila how he did this, he said, "I never went to class." Because he was taking four degrees at the same time, he just read the textbook and took the exam. He was legendary at Cambridge as this super smart graduate student.

I said okay. I'll pay for you out of my funds to be a graduate student at Cambridge for your last year if you come to my lab as a post doc. In nine months he developed this very elegant laser photolysis method to look at single cell sickling, developed the automated algorithm for collecting the data, and then the automated computer algorithms to analyze the data to measure the sickling time for individual cells. Then you could add drugs. He did a drug screen of 2,000 compounds with this technique and he did all of this in eight months. This is like two or three post-docs, each working for four years. He did it all by himself in eight months. Then he walked into my office. He said, "I quit." I said, "What do you mean you quit, Jeffrey?" He said, "Now it's technicians work." He went off to McKinsey, you know, this consulting firm. They had offered him a job when he graduated from Penn, but he decided to get a PhD. They knew him from his undergraduate degree; he didn't need a PhD; they wanted to hire him immediately. And I said, "Why are you going to McKinsey." He said, "Once they see how smart I am, when I consult for some company, they'll hire me as the CEO." He wanted to go right from being a consultant to a CEO of a big company, which he didn't quite do, but apparently, he's high up in McKinsey now.

I've been in contact with him recently because I included him as a co-author on our first paper on drug screening. His method turned out to be too slow. It used 94 well plates. It needs chemicals, which could damage the drugs that we're testing or damage the cells that we're testing. We now have a much more physiologically relevant assay, where we sickle cells just by slowly removing oxygen, as what happens in the tissues, and we can work with 384 well plates. I got lucky when John Tisdale, a hematologist that I collaborate with at NIH, met with Bill Gates and Frances Collins about a year ago, or a little over a year ago, to convince Bill Gates to get interested in sickle cell disease. John Tisdale is able to cure people by stem cell transplantation, and he wants to set up clinics in Africa, where Gates is mainly interested, to cure people of sickle cell disease. He's also developed a gene addition method and is now working on actually editing the gene; he's also been very successful in curing people by gene addition methods, which has been on two 60 Minutes programs- just saw one a week ago. I've actually measured the sickling curves of John's patient who was on 60 Minutes.

We had this assay and the Gates Foundation sponsored the creation of a library of 12,000 compounds for the Scripps Institute at a sub-institute of Scripps called the California Institute of Biomedical Research. Because of John's contact with the Gates Foundation, the Gates Foundation was willing to give me their library, free of charge. This is the most precious library of compounds in the world because it's a library of compounds that have all been given to humans. That's a rate-limiting step in in developing a drug. It is all the toxicology and animal studies before you even get to the phase I clinical trials. It cost on average $2 billion for a drug company to develop a new drug and takes 15 years. The idea of our assay is that we can determine whether a compound - I'm not going to call them a drug because they're not a drug yet, they're a compound - from this library shows sufficient inhibition of sickling in our assay to have therapeutic potential at concentrations found in the serum of patients. Then, we have a drug.

Right now, we have whittled it down to something like 170 compounds of which, if you take into account the fact that 10 percent of oral drugs given to people work at 10 micromolar or larger, we think we have a least a dozen candidates. We don't know what they are yet. We haven't finished the analysis yet, but as soon as we finish Scripps, the Calibr institute, will identify the compounds. Then we can then go on with many basic pharmacokinetic studies and various other things. We can also very rapidly start clinical trials. We have a super smart head of the sickle cell branch here at the NIH, Swee Lay Thein, who's just waiting in the wings for her to write a protocol to submit to the IRB and the FDA to test these drugs on patients. So, that's where we are today. That's where I am today.

Kenneth Durr:

That's an exciting place to be.

William Eaton:

Yes. At 81 years old.

Kenneth Durr:

You mentioned working with scientific directors when we talked about the organization. Talk a little bit about your relationship with different scientific directors over time.

William Eaton:

The first scientific director for me was Ed Rall. I'm going to contrast him with our current scientific director. Ed was a bit of an elitist. He really was only concerned with the top scientists in the Institute. He paid no attention to me whatsoever until somebody, I think it was Chris Anfinsen, told him that they wanted to hire me at Harvard to become the head of biophysics. He got wind of it somehow. Chris went to Harvard for a year and then came back. So, somebody at Harvard must have told him. Ed was followed, I'm trying to think, who followed him. I should know. Jesse Roth, I think followed Ed Rall. I hope I didn't miss somebody. Jesse was this very charismatic guy, and Jesse was an enormously creative administrator.

For example, Michael Levitt, the guy who went on to win a Nobel Prize, spent two summer sabbaticals in my laboratory. He and I became very good friends. I suggested to him at one point that his career would really profit by moving to the United States and leaving Israel. The question was how to get the word out that it would be possible to hire Michael Levitt. The way I did it was I invited Michael to give a seminar at the NIH. I also wanted Michael to come to the NIH. He gave a seminar to the lab, and I went to see Jesse, and he agreed the next day: "sure, we'll hire Michael Levitt." I said, "Well, his wife is an artist and we may have to do something" I was thinking of Ad Bax, about doing something about the wife. I said to Jesse, "We'll have to do something about the wife." He said, "She's an artist. There's an art institute in Baltimore. I think what we can do is get a wealthy Arab to contribute to her fellowship because we could tell them that he is one of the smartest, intelligence officers, which Michael was when he was in the Israeli Army, (or maybe he wasn't, didn't matter), this is Jesse's story. We can get him out of Israel if we can get his wife a scholarship in Baltimore." This is the kind of guy Jesse was.

Our next scientific director turned out to be a disaster. Marvin Gershengorn. I don't want to say anything about it except the whole Institute would agree. We had him for a number of years, and finally Griffin Rodgers did a brilliant job in forcing him out as scientific director. Rodgers deserves a lot of credit for that. He then hired my colleague as an acting scientific director, Ira Levin. Ira did an excellent job. He was replaced by our current scientific director Michael Krause. Michael's been scientific director for about eight years. I'll be embarrassed if I get some of these names or dates wrong that I really should know. [I completely forgot to mention Allen Spiegel, who was Scientific Director for 9 years after Jesse Roth. I only went to his office once in those 9 years, but he did not even let me finish a sentence. So I never went back again and only talked to his deputy, Ira Levin]

I mentioned Ed being an elitist because Michael Krause is the absolute opposite. My only criticism of Krause, who's a brilliant administrator, is that he's too much of a socialist. He worries about everybody in the Institute. He worries about a secretary. Sometimes I get the impression that he worries about the welfare of the secretary as much as the welfare of one of his top scientists. I'm sure that that's a gross exaggeration, but he's such a nice guy that he worries about everybody. He's also carried on this tradition of letting the scientist in our institute proceed with no direction from him. Overall, the quality of scientists at our institute has increased dramatically. When I first came to the NIH, not just the lab that I came to, but many were moribund laboratories. That's not true of any laboratory in our institute. I can't speak for the whole NIH, except that our scientific director Michael Gottesman, whom I've worked with for many years with the IATAP program, has been doing analyses where he shows - I don't know exactly what the statistics are - normalized for the number of principal investigators and dollars per investigator, that the NIH is top in the country over any university. It couldn't be compared to any of the top research universities when I came here. It's evolved into probably the greatest research institution in the world.

When I came to the NIH in 1968, there were tremendous research laboratories that are all gone now. There was DuPont in Wilmington, there was IBM Watson, there was IBM San Jose, there were the great Bell Telephone Laboratories. Now the only ones left are a couple of DOE labs, one of the cheats, is the one at Berkeley, which is as a cash cow for the faculty. They're supposed to be the contractor for the laboratory. There were great laboratories at Oak Ridge. There was Brookhaven. But they're all gone, except for a couple. I asked Earl Lawrence, one of our wonderful executive officers, who retired many years ago, when I met him in a grocery store. I asked him, "Why do you think the NIH is doing so well?" He said, “It is almost a miracle isn't it, because except for the NIH, every other agency of the federal government since the second World War has drifted into mediocrity." It's probably because of the support of the Congress that the NIH has survived. The administrators of the NIH have taken the point of view that Max Perutz took, let the best scientists do what they want. That's how to get the best research done.

Kenneth Durr:

Great place to stop. Thank you so much.

William Eaton:

Okay.

[end of transcript]